Pediatrics and Neonatology (2012) 53, 24–33

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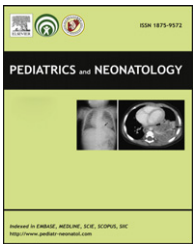

ORIGINAL ARTICLE

Pediatric Renal Transplantation in the Jordanian Population: The Clinical Outcome Measures During Long-term Follow-up Period

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Received Apr 17, 2010; received in revised form Jan 13, 2011; accepted Jan 21, 2011

Key Words
Jordanian;
outcomes;
pediatric;
renal;
transplant

Introduction: Recently, many international studies have suggested that pediatric patients from diverse ethnic origins confront unique challenges for transplantation. Data concerning the efficacy and safety of transplantation for various pediatric renal transplant populations remains limited and are often confounded by immunosuppressive protocols. In one study, we aimed to evaluate the short- and long-term outcomes of renal transplants in Jordanian children in comparison with groups of different nationalities.
Methods: We retrospectively retrieved data for 34 Jordanian children who received kidney transplants from living donors between January 2003 and January 2009. Subsequently, we continued to follow-up with these selected patients at scheduled clinic visits to prospectively collect long-term data for a period of approximately 22 months $\pm$ 15 months.
Results: The patients included in this study ranged between 4 years and 19 years of age. The male/female ratio was 0.79. Glumerulonephritis (35.3%) was the most common cause of end-stage renal disease in the sample of this study; 23.5% had received a preemptive transplant. All patients also received triple immunosuppressive therapy, consisting of tacrolimus (TAC), prednisolone, and mycophenolate mofetil ($n = 26$) or azathioprine ($n = 8$). Furthermore, the rate of acute rejection episodes was lower in the sample of this study than the average rate of many previous studies. The patients' survival rate at 1 year, 2 years and 3 years posttransplant was nearly 100%. The corresponding graft survivals were 97.1%, 94.12% and 91.2% respectively. Beyond three years, one female patient died postgraft loss. This graft loss was mainly attributed to recurrent glomerulonephritis. Strikingly, the prevalence of posttransplant diabetes (PTD) and hypertension was higher than reported international figures. Other adverse events, such as infections, were manageable.

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doi:10.1016/j.pedneo.2011.11.006

Conclusion: The average result of pediatric renal transplantation in Jordan is more successful than the average results of this procedure in many developed countries, especially in terms of early graft function, acute rejection episodes as well as long-term patient and graft survivals. However, additional studies are needed to better characterize pharmacokinetic of TAC and to fully understand those factors that lead to an increased probability of developing conditions like PTD and hypertension.

1. Introduction

There have been several clinical trials,[1–4] retrospective[5–19] and prospective[20–30] long-term follow-up studies, conducted to study the outcomes of renal transplants for recipients who receive various immunosuppressive regimens. Unfortunately, efficacy and safety parameters remain scarce in the pediatric population literature.[31] Although a meta-analysis study has been conducted, the best choice calcineurin inhibitor and the best outcome measure for long-term graft survival are still unresolved issues.[32] Moreover, recent international studies have suggested that adults and pediatric patients of diverse ethnic or racial origins confront different challenges to successful transplantation[2–4,11,16–19,30,33–35] (Table 1). Investigators have provided various possible explanations and multifactorial interplay, including genetic, environmental, immunologic and socioeconomic factors, as well as the variability in prevalence patterns for the etiologies of end-stage renal disease (ESRD) among different populations. In particular, some studies have previously linked socioeconomic criteria, such as low income, a lack of education, a lack of insurance, and noncompliance with immunosuppression therapy, with a significantly adverse contribution to allograft survival rates in certain ethnic minorities.[33,36,37] By contrast, multivariate analysis reports[33] have revealed that socioeconomic factors did not account for these differential outcomes. This conclusion has led some authors to postulate that there may be a higher potential for the association of negative survival rates with physiologic discrepancy, such as a greater prevalence of serious ESRD causes[38–40] (particularly focal glumerulosclerosis) or a higher incidence of cardiovascular risk factors[33,34] (mainly diabetes, hypertension, and hypercholesterolemia) in Asians and African-Americans as compared with Caucasians. Therefore, the real impact of ethnicity and racial disparities on clinical outcomes following kidney transplantation remains a subject of considerable debate. Although the outcome data reviewed in Table 1 are controversial, extrapolation of any of the observed conclusions to the context of the Jordanian population is difficult because previously collected data were obtained by different study designs that included various ethnic/racial groups, heterogeneous ESRD etiologies, or dissimilar age categories. Also, previously collected data have often represented the experience of one institution in one country.

This manuscript describes the details of the first Jordanian study of a sample of pediatric patients who previously received a renal transplant.

2. Patients and Methods

Pediatric renal transplants started in our center (*Royal Medical Services, King Hussain Medical Center, Pediatric Department, Jordan)* in 2003. By 2009, 40 children had received a living donor kidney graft at this center. Four patients died shortly after the operation. These deaths were attributed to vascular thrombosis, recurrence of old disease, or surgical complications. In addition, two patients died in the follow-up period. After obtaining approval from a local ethics committee, this study was initiated in January 2007. We retrospectively retrieved the data from charts/medical records of all patients who received a kidney transplant from living donors between January 2003 and January 2009. Subsequently, we continued to follow-up in monitoring the patients at each of their scheduled clinic visits to prospectively collect long-term data for an average of 22 months $\pm$ 15 months.

A comprehensive data-collection form was designed for the purpose of this study. This form collected information on patients' demographics, anthropometry, pre- and post-transplant medications (such as antihypertensives, insulin, iron, calcium and vitamin supplements, etc.), etiology of ESRD, dialysis modality (peritoneal dialysis, hemodialysis, or none), date and age of transplant, donor source, recipient baseline medical, and laboratory evaluations. The primary follow-up endpoints included the incidence of acute or chronic rejection, nephrotoxicity, and patient and graft survival. Acute rejection in this study only included biopsy proven episodes, which were defined as a rapid and unexplained rise in serum creatinine (SrCr) of at least 0.3 mg/dL/day above the considered baseline posttransplant; the use of high-dose steroid therapy or antibody treatment was clearly associated with subsequent improvement of renal function. If signs and symptoms remained unresolved after "pulse" corticosteroid (methylprednisolone of 500 mg intravenous infusion over 2 hours for 3- to 5-day period), subsequent therapy was based on the severity of rejection with antithymocite globulin (ATG) being reserved to treat the most severe rejections.

Although drug-induced nephrotoxicity was confirmed in the presence of high tacrolimus (TAC) whole blood concentrations with other typically associated clinical manifestations including raised SrCr ($>$ 0.15 mg/dL/day) and blood urea nitrogen (BUN) levels, hyperkalemia, hyperuricemia, and decreased fractional excretion of sodium, this was promptly resolved after TAC dose reduction. Chronic rejection was confirmed based on histological findings for renal core biopsy. Graft loss was defined as

Table 1 Comparisons of major renal transplant outcomes among various ethnic/ racial groups (literature review).

Author (date)	PoP	Study design	Ethnic or Racial group	Outcomes (%)								
				1year PS	5 years PS	1year GS	5 years GS	AR	DGF	CR	PTD	PTH
Neylan et al (1998)[4]	A	CT	African-American	94.6 ^{NS}	—	91.1 ^{NS}	—	23.2 ^{NS}	50 ^{NS}	—	36.6*	57.1*
			Caucasian	94.7		90.4		29.8	45.6		12.2	49.1
Hauser et al (1998)[3]	A	CT	Caucasian	92.5	—	82	—	23.5	—	—	—	—
Trompeter et al (2002)[2]	P	CT	Caucasian	97	—	90.3	—	36.9	23.3	—	3	68.9
Loucaidou et al (2004)[17]	A	R	Indo-Asian	—	70^{NS}	—	NS	NS	—	—	—	—
			Non- Indo-Asian		83							
Pallet et al (2005)[33]	A	Pr	African European	98^{NS}	93^{NS}	92^{NS}	83^{NS}	31^{NS}	44*	—	—	—
			Caucasian	97	92	92	83	30	30			
Dooldeniya et al (2006)[34]	A	Pr	Indo-Asian	—	NS	—	NS	39.1^{NS}	30.4^{NS}	—	10.9*	NS
			Caucasian					53.3	36.7		3.3	
Weber et al (2006)18	A	R	Canadian	—	50*	—	66^{NS}/26 *,†	NS	30^{NS}	—	16*	—
			Aboriginal		75		67/47		24		8	
			Caucasian									
Omoloja et al (2007)19	P	R	African-American	—	—	—	59.9*	—	—	—	—	—
			Caucasian				77.7					
Vasudevan et al (2008)[11]	P	R	Indo	100	94	94	82	18	21.2	18.2	—	75
OPTN-SRTR (2008)[30]	A / P	Pr	Black	84.9*	—	94.6^{NS}	71.8 /43.7*,†	—	—	—	—	—
			White	80.6		95.7	81.7 /59.6					
			Asian	95.7		97.4	89 /65.1					
			Hispanic/ Latino	90.1		96.2	84.6 /64					
Hau Shu et al (2008)[16]	P	R	Chinese	100	92.1 /71.4†	98.4	88.9 /68.3†	30.2	—	—	4.8	41.3
Matsuda-Abedini et al (2009)[36]	P	R	British Columbia	—	87.5*	—	—	33.3 ^{NS}	0.04^{NS}	50*	—	—
			Aboriginal		95.6			39.3	0.007	26.7		
			Non-Aboriginal									
Oztek et al (2009)[35]	P	R	Austria	100 ^{NS}	100 ^{NS}	88.2 ^{NS}	88.2 ^{NS}	20 ^{NS}	—	—	—	—
			Immigrant	97.2	93.7	92.9	86.1	37				
			Native									

PoP, population; A, adults; P, pediatrics; CT, clinical trial; Pr, prospective follow-up; R, retrospective analysis; PS, Patient Survival; GS, Graft Survival; AR, acute rejection in 1st year; DGF, delayed graft function; CR; chronic rejection; PTD, post-transplant diabetes; PTH, post-transplant hypertension; NS; no statistically significant difference.

* statistically significant.

† 10-years data.

a condition in which any other modality of renal replacement therapy is required.

Safety was assessed based on the described adverse events and routine laboratory evaluations, including Full Chemistry and Hematology tests. In addition, vital signs, body weight, and height were continuously recorded.

Glomerular filtration rate (GFR) was estimated based on Schwartz's formula[41]:

GFR (mL/min/1.73 m^2) = K × height (cm)/SrCr (mg/dL), where K factor was 0.55 for all children (boys and girls) aged 2 to 12 years and girls 13 to 21 years, whereas it was 0.7 for boys ranging from 13 to 21 years of age.

3. Immunosuppressive Regimens

The standard immunosuppressive protocol for pediatric renal transplant at our center considered TAC, rather than cyclosporine, as the primary calcineurin inhibitor due to findings that suggest its superior efficacy and comparable safety profiles in various pediatric populations.[1,3,4] The initial TAC dose was to be administered within 24 hours of transplantation. Its recommended dosage was 0.3 mg/kg/day to achieve trough concentrations of between 10 ng/mL and 20 ng/mL during the first month after transplantation, and 0.1 mg/kg/day thereafter to achieve trough levels of between 5 ng/mL and 10 ng/mL. Steroids were administered preoperatively in an intravenous dose of 300 mg/m^2, and then orally, tapering from 60 mg/m^2 per day to 15 mg/m^2 every other day within 3 months. Mycophenolate mofetil (MMF) or azothioprine were also combined with any previous therapy at a dose of 600 mg/m^2 per day and between 50 mg/day and 100 mg/day, respectively.

TAC whole blood trough concentrations were monitored throughout the follow-up visits and the assay was performed using a microparticle enzyme immunoassay (Abbott IMx, Abbott Laboratories, Abbott Park, IL, USA).

4. Statistical Analysis

All of the collected data were coded, entered and analyzed using SPSS© software (version 17.0; SPSS Inc, Chicago, IL, USA). The data were generally analyzed and expressed as the mean ± standard deviation for continuous variables and as the percentage of the population for categorical variables.

A student *t* test and analysis of variance test (with Tukey's post-hoc test*)* were employed for paired and multiple comparisons of renal function measurements, TAC serum levels, dosage requirements at different points in time using the GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, CA, USA), respectively. A p value <0.05 was considered to indicate statistical significance.

5. Results

A total of 34 pediatric renal transplant recipients at our center (between 2003 and 2009) were included in this cohort study. They all received transplants from living donors. The baseline demographic and clinical profile criteria are summarized in Table 2. The sample patients' ages ranged between 4 years and 19 years of age. The male/female ratio was 0.79. Six patients (3 males, 3 females) were below 9 years of age at the time of transplantation. Glumerulonephritis (35.3%) was the most

Table 2 Demographic and baseline clinical characteristics of renal transplanted pediatrics.

Variables	
Number of patients	34
Age (yrs) at time of transplantation (mean ± SD)	11.3 ± 2.9
< 13 years	21 (35.6)
≥ 13 years	13 (22)
Gender	
Male, n (%)	15 (44.1)
Female, n (%)	19 (55.9)
Weight (kg) at time of transplantation (mean ± SD)	29.7 ± 10
Height (cm) at time of transplantation (mean ± SD)	128.6 ± 15.6
Donor, n (%)	
Father	11 (32.4)
Mother	16 (47.1)
Brother	1 (2.9)
First degree relative	2 (5.9)
Living unrelated	4 (11.8)
Modality of dialysis, n (%)	
HD	21 (61.8)
PD	3 (8.8)
HD and PD	2 (5.9)
Duration of dialysis, months (mean, range)	
HD	15.7 ± 3.5
PD	21 ± 7.9
HD and PD	20 ± 4
Pre emptive transplant, n (%)	8 (23.5)
Primary reason for transplant, n (%)	
Congenital hypodysplasia of the kidney	11 (32.4)
Hereditary nephritis	5 (14.7)
Reflux nephropathy	6 (17.6)
Glumerulonephritis	12 (35.3)
Pre-transplant hypertention, n (%)	28 (47.5)
SBP (mmHg)	119 ± 20.5
DBP (mmHg)	78.8 ± 15.3
GFR prior transplantation (mL/ min/ 1.73 m^2, mean ± SD)	14.9 ± 10.4
Pre-transplant clinical laboratory (mean ± SD)	
Serum creatinine (mg/dL)	6.4 ± 2.8
Serum potassium (meq/ L)	4.7 ± 1.3
BUN (mg/ dL)	72.5 ± 42.9
Glucose (mg/ dL)	138.8 ± 174.6
Hemoglobin (g/ dL)	8.6 ± 1.8
Hematocrit (%)	25.9 ± 5.7

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; GFR, glomerular filteration rate; BUN, blood urea nitrogen.

common cause of ESRD in our population, followed by congenital hypodysplasia (32.4%). Focal segmental glomerulosclerosis (FSGS, $n = 5$), membranoprofilerative glumerulonephritis (MPGN, $n = 6$), and hemolytic uremic syndrome ($n = 1$) were the main etiologies among glumerular diseases prevalent in our cases.

5.1. Immunosuppressive therapy

All 34 patients received triple immunosuppressive therapy (Table 3), which consisted of TAC and prednisolone, MMF ($n = 26$) or azathioprine (AZA; $n = 8$). However, MMF was substituted with AZA in five cases, and MMF replaced AZA in another four cases due to intolerable adverse events encountered within the first year.

Initially, the mean daily dose of TAC (mg) on the 1st day (initial dosing), 7th day, 14th day, 1 month, 1.5 months, 2 months, 3 months, 6 months, 9 months, and 12 months were respectively as follows: 7.2 ± 2.2, 7.4 ± 2.3, 7.3 ± 2.3, 7.3 ± 2.8, 7.1 ± 2.9, 6.6 ± 2.6, 6.6 ± 2.4, 6.1 ± 2.1, 6.1 ± 2.1, and 6.1 ± 2.2.

The maximum mean for the total daily doses of TAC required to achieve target blood concentrations (10—20 ng/mL) was discerned during the first month of therapy, and gradually in the subsequent follow-up period with the lowest mean dose requirements to attain target concentration (5 ng/mL) observed at a 3-year interval (5.7 ± 1.5 mg/day). Figure 1 depicts the mean trough concentrations of TAC during the follow-up period.

The mean daily steroid dosage decreased from 19.6 mg/day in the first month to 5.2 mg/day in the twelfth month. All patients continued to take steroids at a low dose throughout the study observation period.

5.2. Patient and graft survival

The patients' survival rate at 1 year, 2 years, and 3 years was 100%. Beyond 3 years, one female patient died post-graft loss after reinstituting hemodialysis 5 months before her death. Her death was attributed to further complications with the subsequent development of diabetes, cytomegalovirus (CMV) and Candida infections.

Table 3 Immunosuppressive therapy.

Drug	Dose (mg/ day)* (mean ± SD)	Range (mg/ day)	N, (%)
TAC	7.2 ± 2.2	3-14	34 (100)
Prednisolone	40.9 ± 16.1	5-60	34 (100)
MMF	883 ± 284.2	500-1500	30 (88.2)
AZA	75 ± 21.9	50-100	13 (38.2)
TAC + MMF + steroids			26 (44.1)
TAC + AZA + steroids			8 (13.6)
Substituted MMF with AZA			5 (14.7)
Substituted AZA with MMF			4 (11.8)

TAC, tacrolimus; MMF, mycophenolate mofetil; AZA, azathioprine.
* initial starting dose.

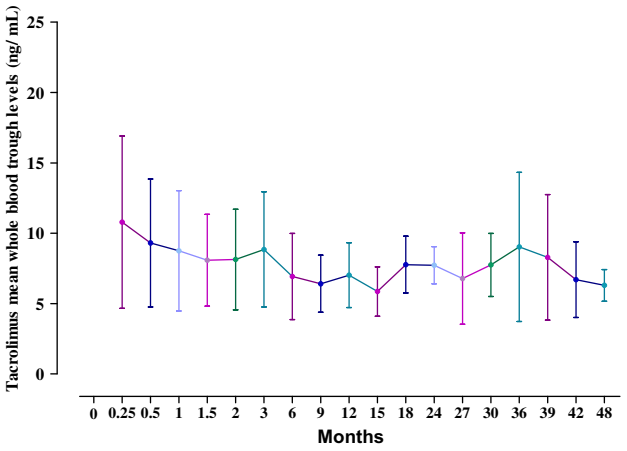

Figure 1 Mean Tac whole blood trough levels during follow-up post renal transplantation.

The graft survivals at 1 year, 3 years, and 4 years were 97.1%, 94.12%, and 91.2% respectively. In total, three grafts were lost due to a poorly functioning graft subsequent to acute tubular necrosis (ATN), recurrent Mesangiocapillary glomerulonephritis (MCGN) and chronic rejection, respectively. However, the first two cases remained on hemodialysis for the rest of the study period. The chronic rejection case died 6 months later.

5.3. Acute rejection

During the first year, five acute rejection episodes were experienced in five patients (14.7%). Only one of the episodes occurred in a child who had received a preemptive transplant. Two episodes were encountered on the second posttransplant day due to severe renal artery stenosis and ATN secondary to recurrent MPGN. Although one of the acute rejections occurred on 24th day, that patient's renal biopsy revealed vascular rejection associated with recurrence of FSGS. In the 4th month, another patient experienced acute rejection due to acute renal failure secondary to ureteral obstruction; this condition was managed by inserting a double-J catheter while inducing intensive steroid therapy. The final acute rejection was reported in the 11th month but the etiology was unknown. The average TAC trough level before rejection was 5.93 ng/mL ± 0.8 ng/mL, which was considered below the optimal target, particularly in the period of the initial two episodes.

Four of the previous episodes were treated with pulses of methylprednisolone of 500 mg intravenous infusion over 2 hours for 3 to 5 days with or without ultrafilteration, followed by the tapering of steroids. However, ATG was required to be initiated at a dose of 200 mg for 5 days in one corticosteroid-resistant ATN case which was partially responsive.

5.4. Chronic rejection

During the follow-up, five patients (14.7%) displayed a progressive irreversible rise in SrCr above 2.5 mg/dL, and thereafter progressed to chronic allograft nephropathy.

One case was treated with ATG but remained unresolved. Three patients developed chronic rejection and lost their grafts, subsequently returning to dialysis.

5.5. Renal function

As markers for renal function, SrCr and BUN concentrations were measured routinely in each scheduled clinic visit and throughout the follow-up study period. The mean values for renal function parameters at different time points are shown in Table 4.

At one year posttransplant, SrCr was normal in 21 patients (35.6%), five patients (8.5%) had SrCr levels between 1 mg/dL and 1.39 mg/dL, six patients had SrCr levels between 1.4 mg/dL and 2 mg/dL and only 6% were higher than 2 mg/dL. In regard to BUN, 22 (37.3%) patients had levels below 20 mg/dL, nine patients had levels between 20 mg/dL and 44 mg/dL and only 3 (8.8%) had elevated urea levels ($>$ 44 mg/dL). In regard to GFR, no significant difference was found between younger ($<$ 13 years old) and older children ($\geq$ 13 years) in our population at any given time (Figure 2). The maximum improvement in GFR was observed at Day 14 posttransplant, and it was maintained with minimal changes throughout the initial 18 months. Although the mean GFR at Month 24 (73.6 ± 26.6) and Month 36 (80 ± 16.3) further declined compared with previous measurements, particularly in the first year, these deteriorations did not reach statistical significance ($p > 0.05$, ANOVA test).

5.6. Adverse events

The incidence of adverse events is summarized in Table 5. A total of 28 (82.4%) patients experienced at least one adverse event during the first year posttransplant. Of the adverse events, 42 (60%) required hospitalization and management for a period ranging between 2 days and 30 days. Other adverse events were sometimes managed by drug therapy on an outpatient basis (28.5%), or no action was required to be taken (12.9%). The most frequently reported adverse events were urinary tract infection, hyperkalemia, and respiratory infections. CMV was confirmed in three patients who were successfully treated with acyclovir or gancyclovir. Diarrhea occurred in five patients, and their conditions improved after discontinuation, dose reduction or withhold of MMF for one week.

New-onset insulin-dependent diabetes mellitus, defined as insulin use for $\geq$ 30 consecutive days in previously nondiabetic patients, was reported for four patients (11.8%) who continued to use insulin until the end of the observation period. Newly diagnosed hypertension requiring two or more antihypertensive medications was encountered in two patients (5.9%). Nephrotoxicity was reported in four patients, which was associated with elevated TAC trough concentrations (mean, 19.9; range, 15–24.4 ng/mL) and raised SrCr (>3 mg/dL).

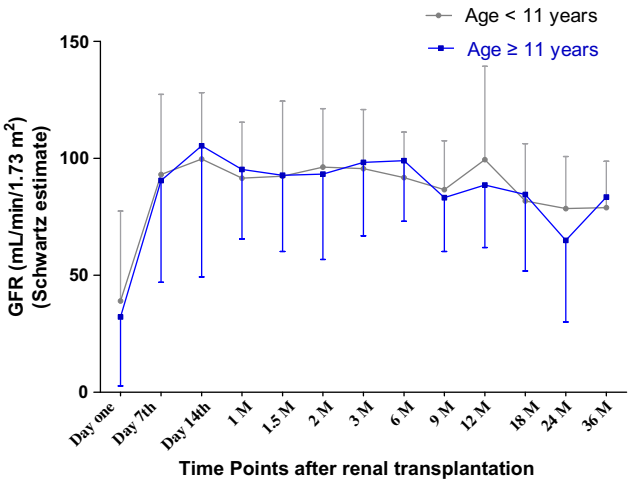

Figure 2 Mean GFR ($\pm$ SD) during follow-up post renal transplantation according to age groups.

6. Discussion

In the present cohort, we recall a previous national survey which had expressed a lower prevalence of pediatric ESRD in Jordan (14.5 per million children less than 14 years of age) as compared with similar European and American reports.[42] Yet the registered mortality rate among our ESRD series at that time was 52.2%. This figure was considered to be very high in comparison with an average mortality rate of 7% as reported in the USA.[43] This high mortality rate is attributed to various causes but mostly due to the delay in diagnosis and hence commencement of dialysis modality, as well as the relatively recent incorporation of a pediatric renal transplantation program in Jordanian healthcare services (mainly in 2003), as compared with the earlier foundation of such programs in many developed countries. Herein, we describe the cumulative Jordanian experience

Table 4 Serum creatinine, BUN, and estimated graft function on as calculated by Schwartz formula after transplantation.

Time after transplantation*	Serum creatinine (mg/dL)	BUN (mg/dL)	GFR (mL/ min/ 1.73 m^2)
Month 3	0.84 ± 0.33	19 ± 8.2	96.76 ± 27.5
Month 6	0.84 ± 0.3	17.3 ± 6.4	94.8 ± 22.2
Month 9	0.94 ± 0.3	18.7 ± 5.9	85.3 ± 21.4
Month 12	1.15 ± 1.51	21 ± 15.5	95.4 ± 35.5
Month 24	1.2 ± 0.9	26.3 ± 18.5	73.6 ± 26.6
Month 36	1.03 ± 0.3	31 ± 22	80 ± 16.3

*$P > 0.05$; statistical significance of mean difference between repeated mean measurements is determined by ANOVA test and Post Hoc-Tukey's test. Abbreviations: BUN, blood urea nitrogen; GFR, glomerular filteration rate.

Table 5 Adverse events induced during the follow-up period.

Adverse event	N, (%)
Gastrointestinal	
Diarrhea	5 (14.7)
Constipation	1 (2.9)
Abdominal pain	2 (5.9)
Viral gastritis	4 (11.8)
Bacterial gastroenteritis	3 (8.8)
Cardiovascular	
Hypertension	2 (5.9)
Hypertensive encephalopathy	1 (2.9)
Chest pain	1 (2.9)
Infections	
Urinary tract infection	12 (35.3)
Pyelonephritis	1 (2.9)
Respiratory infection	6 (17.7)
Sepsis	2 (5.9)
Acute otitis media	2 (5.9)
Gingivitis	1 (2.9)
Fungal	
Candida	4 (11.8)
Viral	8 (23.5)
Cytomegalovirus	3 (8.8)
Herpes zoster	3 (8.8)
Herpes simplex	5 (14.7)
H. influenza	2 (5.9)
Varicella zoster	2 (5.9)
Dermatological	
Skin fungal infection	3 (8.8)
Skin viral infection	5 (14.7)
Skin bacterial infection *(S. aureus, S. epidermis)*	1 (2.9)
Allergic rash	1 (2.9)
Metabolic	
Diabetes	5 (14.7)
Diabetic ketoacidosis	2 (5.9)
Hyperkalemia	9 (15.3)
Hypokalemia	5 (8.5)
Nephrologic	
Nephrotoxicity	4 (11.8)
Hydronephrosis	2 (5.9)
Recurrence of old disease	2 (5.9)
Hematologic	
Anemia	4 (11.8)
Thrombocytopenia	1 (2.9)
Leucopenia	3 (8.8)
Neurologic	
Tremor	1 (2.9)
Organic psychosis	1 (2.9)
Dehydration	1 (2.9)
Visual disturbances	2 (5.9)
Lower limbs edema	1 (2.9)
Dental abscess	1 (2.9)

in pediatric renal transplantation with its updated clinical outcomes.

According to previous clinical trials, retrospective analysis and longitudinal prospective follow-up studies were conducted in pediatric renal transplant from live donors encompassing various ethnic groups including: American,[7,24] Canadian,[1,2,38] European,[3,10,14,15,25,35] South Asian,[5,6,16,20,26–28] Indian,[11] Turkish,[8,12,13] and Arabic[9] populations. These studies reported that survival rates at 1 year, 3 years, 5 years and 10 years ranged between 92.5% to 100%, 91% to 96.4%, 92% to 98.6%, and 71.4% to 95%, respectively. The corresponding graft survival rates for these studies were as follows: 82% to 100%, 78% to 90%, 67% to 100%, and 45% to 68%, respectively. In comparison, the findings of this study report excellent patient and graft survival findings (of 97% and 91.2%, respectively) over a median follow-up period of 18 months (6 months to 64 months).

Early acute rejection episodes were seen at much lower rates in our pediatrics (14.7%) than in most previous multinational data[2,3,5,7,12,14,16,22,26,28,35,36] (25% to 54%). Yet this finding is comparable to incidences described in some other ethnic minorities.[6,8,11,13,20,27] Interestingly, all observed episodes in the current series, except for one, were steroid sensitive, which was completely reversed by methylprednisolone therapy. A possible explanation for this finding is that all of our patients were treated with TAC, rather than cyclosporine; the former treatment was demonstrated to have greater efficacy in preventing acute steroid-insensitive rejections.[1,3] Another important factor which most probably accounts for the lower acute rejection rate in these patients is the protective effect of a living donation, especially from many of the sampled patients' parents. A similar impact of donor source overriding the factor of ethnicity has been observed in African-American and Austrian or Canadian immigrant patients receiving kidneys from living donors; they demonstrated better outcomes as compared with analogous groups who received transplants from deceased donors.[33,35,36]

Similar to the previous experience of the Canadian and Australian centers,[36] the higher incidence of glomerulonephritis as the primary etiology of ESRD among our population may have significantly contributed to our graft losses. Indeed, the three patients who lost their graft in our series had MPGN ($n = 1$), RPGN ($n = 1$), or celiac disease as the main cause of their ESRD. In fact, a previous registry study involving 1505 patients[44] had reported that recurrent glomerulonephritis was the third most frequent cause for graft loss, where the risk of loss due to recurrence was estimated to increase from 0.6% in the first year to 8.4% in the tenth year, posttransplant. Retransplantation was not performed in any of our patients who lost their graft, due to concerns of recurrence ($n = 2$) or death ($n = 1$).

Preemptive transplantation has been the most preferred treatment modality for pediatric ESRD for several reasons. However, this preference is mainly due to a reported favorable effect on growth and cognitive development and avoidance of severe long-term uremic symptoms and morbidities.[45] Moreover, previous studies revealed that preemptive transplant was associated with either more promising[46] or similar outcomes for graft survival after

transplantation.[47] In spite of all these advantages, many patients will require dialysis before transplantation, due to the unavailability of a suitable donor.[45]

Most of our cohort has undertaken hemodialysis, peritoneal dialysis, or both modalities prior transplant (76.5%) for an average of 16 months $\pm$ 15 months and only 23.5% received preemptive transplantation. This frequency is in accordance with the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) report of 25% transplanted preemptively.[46] This could be a possible explanation for the higher prevalence of older age ($>$ 9 years; 82.4%) in the current transplantation report. Alternatively, this could be a positive factor to improve future outcomes because both patient and graft survival rates are higher in children over 5 years of age[48].

Unexpectedly, the outcomes of our preemptive transplants (23.5%) were comparable with their nonpreemptive counterparts in terms of acute rejection (12.5% vs. 15.4%) and patient survival (100% vs. 96.2%). However, the frequencies of drug-related adverse events (87.5% vs. 80.8%), and particularly the new onset of diabetes (25% vs. 7.6%), were markedly higher in the preemptive transplant recipients. Yet these results might be preliminary due to the unequal sample sizes in the two counterparts; before we draw conclusions, we must await further validation from larger groups and cohorts.

In regard to graft function expressed by GFR and SrCr, this improved drastically within the first 14 days posttransplant and its stability was maintained throughout the observation period. Even after three years, it sustained higher[1,2,4,10] or comparable[13,49] levels with those achieved by other populations from large centers. As noted, younger and older age groups in our series (Figure 2) fared similarly with respect to their improvement and stability of graft function.

The development of posttransplant diabetes (PTD) has mostly evolved in adults posttransplant,[13,16,23,50] although at a variable range (from 3% to 46%) and at a lower frequency in pediatrics (between 3% and 5%). This complication has been predominantly attributed to the diabetogenic effect of both steroids and TAC-based immunosuppressive therapy.[2,4] Surprisingly, the prevalence of PTD among our series was noted to be high (14.7%) as compared with the NAPRTCS study[23] and other pediatric studies,[2,16] although it is still comparable with some surveys that studied diverse ethnic populations.[6,20,26] A few reports verified the onset of PTD in association with an increased risk of acute rejection[13,16,23,50] or diabetic ketoacidosis,[51] leading to subsequent graft loss. Nevertheless, the coincidence of these complications was only noted in one diabetic female patient among our cohort. Another patient experienced diabetic ketoacidosis but this patient had preserved kidney function and graft survival. The high prevalence of PTD in our cohort may be attributed to a number of clinical variables suggested by previous reports on different ethnic groups,[4,18,23,34] including positive family history, obesity, increased diabetogenic effect of TAC in combination with MMF (vs. cyclosporine and AZA), high TAC trough levels, and ethnicity. However, we do not yet know which of these variables would have a quantitatively higher and/or independent impact on increasing glucose abnormality in this cohort.

Hypertension, which is deemed to cause deleterious effects on kidney functioning, remains a frequent problem posttransplant as well[2,8,10,11,15,16] (25% to 67%). In our study, pre- and posttransplant hypertension (PTH) was diagnosed in 82.4% and 5.9% of the patients, respectively. About 85% of our series were either managed by one (14.7%) or received a mean of 2.3 $\pm$ 0.9 (70.5%; range, 2–4) antihypertensive medications; the mean systolic blood pressure (SBP)/ diastolic blood pressure (DBP) by the end of 3 years was 122/68 mmHg ($\pm$ 6.8/12.7). Again, the prevalence of PTD and PTH were higher than previously reported international figures.[2,8,10,11,15,16,23] It is important to point out that it is imperative to resolve the latter two risk factors to avoid further fatal and nonfatal cardiovascular events, which are extensively reported in pediatric renal transplant recipients,[15,52–54] if these complications continue to manifest.[15,51–53] Actually, increased total mortality has been mostly attributed to the stronger negative impact of propagating cardiovascular risk factors, rather than graft loss itself.[15,51–53] Accordingly, demographic and clinical patient variables related to their prominent incidence in our pediatric population should be examined in future surveys.

Despite the fact that most of our patients experienced side effects, none of the observed effects were life threatening. The urinary and respiratory infections that were experienced by patients in our cohort are also frequently reported in related studies, from 57%[9] and 52%[11] respectively. In our results, these infections occurred at lower rates (38% and 17.7%, respectively). Yet again, all cases were successfully managed. Complicated infection with polymerase chain reaction (PCR) confirmed CMV was described to arise at a variable range from 3.6% to 20% of pediatric renal transplant.[8,10] In our series, it was 8.8%. At our institution, all CMV cases were efficiently controlled with a suitable antiviral treatment protocol.

Noncompliance with immunosuppressive drugs, which is more prevalent in children, has been described as having a strong correlation with acute and chronic rejections.[8,11,16,27] Perhaps the favorable outcomes in the current study can be somewhat justified by the perfect compliance of our children to immunosuppressive therapy, which was confirmed during their clinic visits. In addition, the patients were provided with a continuous therapeutic drug monitoring service to maintain TAC target concentrations. However, in the present paper, we have not analyzed the impact of initial patient parameters and other contributing biological factors that could potentially alter the initial or ultimate TAC dosage requirements[22,28,29,55]; these details remain to be tailored in our upcoming population pharmacokinetic modeling study.

In conclusion, despite the high prevalence of PTD and PTH, the current pediatric renal transplant cohort within the main Jordanian pediatric center has progressed well. Moreover, the overall survival outcome of the cohort compares favorably with counterparts in developed countries in respect to both efficacy and safety. Other important issues underlying the individualization of current immunosuppressive therapy (TAC, steroids, or MMF) with the aim of reducing the incidence of PTD and PTH, while still managing to avoid compromising the survival outcomes due to underimmunosuppression, need to be fully addressed in

our future multivariate study. Less serious adverse events, including gastrointestinal and hematological infections that are frequent among different populations, were easier to control. However, there is still a need for more comprehensive detection and care programs.

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